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Disease-a-Month

Use of Anticoagulant and Fibrinolytic Agents

KENNETH M. MOSER

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Disease-a-Month

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Use of Anticoagulant and Fibrinolytic Agents

KENNETH M. MOSER

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TO DISCUSS the therapy of thromboembolism is to stoke the fires of controversy. The fuel of such fires is uncertainty, and the topic of thromboembolism provides this fuel in abundance. The massive literature dealing with the thrombotic disorders and their therapy offers written testimony to the heat which this debate has generated (1, 2).

The widespread and intense concern with thromboembolism is understandable, for few conditions rival thrombotic events as causes of medical morbidity and mortality. Pulmonary embolism, venous thrombosis and arterial occlusion are our daily companions in medical practice. In each of these acute thrombotic situations, the physician must make prompt therapeutic decisions. Unfortunately, these decisions must often be based on evidence that is inconclusive and controversial.

The roots of the therapeutic dilemma surrounding thromboembolism reach deep. Review of the literature quickly discloses that question surrounds the pathogenesis, the diagnostic criteria and the prognosis of the thrombotic diseases. In any disease not subject to precise diagnosis, prognosis and etiologic definition, the treatment employed is characteristically both variable in type and difficult to evaluate.

The reader might surmise correctly from this introduction that

any discussion involving the anticoagulant drugs and the fibrinolytic agents must reflect to some extent the discussant's personal opinion and experience if a chaotic presentation is to be avoided. Indeed, total objectivity would be virtually impossible because few "established" or "absolute" standards exist. Therefore, this monograph will not—and could not—supply definitive answers to all questions regarding antithrombotic therapy. The aim has been to present current knowledge about the actions of the available antithrombotic drugs and to review the conditions in which their appplication should be considered. Whether the agents are indicated, the choice of drug and the method of administration must remain decisions of the individual physician facing a specific situation. The information provided can only guide the physician by indicating what is known about these agents and, perhaps more important, what is still unknown.

ANTITHROMBOTIC AGENTS AVAILABLE

Three major categories of antithrombotic drug are currently available for general use: (1) the so-called *prothrombinopenic (PTP) drugs* of the coumarin or indandione types, (2) *heparin* and heparin-like compounds and (3) fibrinolytic agents such as fibrinolysin (plasmin), streptokinase and urokinase. While these three types of agents differ in mechanism of action, composition, route of administration and specific therapeutic purpose, they share four common features: (1) each is supposed to exert a favorable effect on the thromboembolic disorders; (2) rational and safe use of any of them demands familiarity with their behavior in vivo and the means for estimating their effect on the coagulation mechanism; (3) controversy surrounds the value of these drugs in specific thrombotic disorders, as well as the dosage regimens of choice; and (4) continuous efforts are being made to develop safer, more effective, drugs of each type.

The Prothrombinopenic (PTP) Drugs

The unfortunate hemorrhagic demise of a number of heroic cows following ingestion of spoiled sweet clover ultimately led to the discovery that certain members of the coumarin family

were capable of profoundly altering the coagulation mechanism. When the culprit in this saga of mysterious bovine death was identified specifically as bishydroxycoumarin (Dicumarol), a new therapeutic era in medicine began.

In the more than 20 years which have passed since the isolation and synthesis of bishydroxycoumarin, a great number of other coumarin derivatives have been synthesized and evaluated.

TABLE 1.—PROTHROMBINOPENIC DRUGS CURRENTLY AVAILABLE FOR GENERAL USE

A. COUMARIN DERIVATIVES:

Generic Name	*Commercial Name(s)*
Bishydroxycoumarin	Dicumarol
Warfarin sodium	Coumadin sodium, Warcoumin
Ethyl biscoumacetate	Tromexan
Phenprocoumon	Marcumar
Acenocoumarol	Sintrom
Cyclocoumarol	Cumopyran

B. INDANDIONE DERIVATIVES:

Phenindione	Hedulin, Danilone, Eridione
Diphenadione	Dipaxin

In addition, another family of prothrombinopenic agents, the indandione drugs, has been discovered. While many PTP agents have fallen by the clinical wayside, the list of those in current use is still considerable (Table 1).

MECHANISM OF ACTION.—The label "prothrombinopenic agent" is actually an archaic and somewhat misleading one, since it implies that these drugs act solely by depressing the plasma prothrombin concentration. However, prothrombin is but one of several clotting factors whose hepatic synthesis is impaired by the administration of these compounds. The term "prothrombinopenic" has gained popular favor because the first test used to measure the in vivo activity of these compounds was unfortunately labeled the one-stage *prothrombin time.* Actually, the "prothrombin time" of Quick simply measures the speed of clotting which follows the addition of excess thromboplastin and calcium to oxalated fresh plasma (3). Therefore the test will reflect deficiency of any factor involved in the second or third

stages of coagulation—i.e., the formation of thrombin, and the conversion of fibrinogen to fibrin. At least three factors play an important role in the formation of thrombin: prothrombin itself, factor V (Ac-globulin, accelerin, labile factor) and factor VII (SPCA, convertin, stable factor, autoprothrombin II). In addition, there is evidence suggesting that another substance (factor X, Stuart factor) may be involved in thrombin formation. The presence of thrombin antagonists (such as heparin) also will prolong the "prothrombin time." Finally, deficiency or abnormality of fibrinogen can influence the results of the test (4).

Therapeutic doses of the coumarin or indandione drugs depress at least two "clotting" factors which influence the prothrombin time—namely, factor VII and prothrombin itself. Most studies have indicated that factor VII activity is lowered first and most severely with reduction to zero commonly observed. Prothrombin concentration usually falls a bit later (24–48 hours) and stabilizes at 15–30% of normal. It is also likely that factor X (Stuart factor) is depressed. Factor V and fibrinogen concentrations are not altered by these drugs (5–7).

The PTP drugs have an additional effect which is not detected by the one-stage prothrombin time. They depress PTC (plasma thromboplastic component, Christmas factor, autoprothrombin I). Since this factor is involved in the *first* stage of coagulation (thromboplastin formation), one-stage prothrombin tests are not altered as thromboplastin is supplied in performance of the test. PTC is quite markedly reduced (often completely eliminated) in patients receiving most of the "prothrombinopenic" drugs. It returns to normal levels rather sluggishly after cessation of therapy. This reduction in PTC has raised several interesting questions; for example: Are those drugs which reduce PTC more effective in preventing thrombosis than those which do not? Is behavior of this factor responsible for the imprecise correlation between prothrombin time and the development of bleeding? Are agents which reduce PTC more dangerous because administration of vitamin K_1 does *not* restore this factor to normal as rapidly or as completely as factor VII and prothrombin (8)? These questions cannot be answered with authority at this point, although it does appear that compounds

which do reduce PTC are neither more effective nor more dangerous than those which do not (6).

PROTHROMBIN TIME DETERMINATIONS.—The PTP drugs cannot be used safely or properly without reliable facilities for determination of the prothrombin time. This would be akin to using insulin without periodic checks of the blood or urine sugar level. Unfortunately, a prothrombin time is somewhat more difficult to interpret than a blood or urine glucose value. *The significance of any absolute prothrombin time value is dependent on several factors,* including the individual performing the test, the type of prothrombin time test used, the thromboplastin employed and the methods used for reporting results.

Once a technician has been adequately trained in performance of a prothrombin time determination, his own duplicate results should agree quite closely. However, prothrombin times obtained in the same laboratory by another equally well-trained subject may consistently be longer or shorter. Therefore the physician should pay more attention to the *relationship* between control and patient values than to any *absolute* prothrombin time value.

Even more important is the knowledge of the type of prothrombin test being carried out. Among the tests available in addition to the Quick procedure are variations of the one-stage method utilizing various plasma dilutions, the two-stage method of Ware and Seegers (9) and the Owren P & P method (10). In my opinion, the standard one-stage method remains the most suitable for clinical use. Its simplicity leaves less room for technical error. Furthermore, it reflects the hazard of bleeding more accurately than the two-stage method, which is rather specifically dependent on *prothrombin* concentration alone. Since the PTP drugs reduce both prothrombin and factor VII levels, the two-stage procedure may give a false sense of security and lead to overdosage when factor VII reduction exceeds or precedes prothrombinopenia (11).

Variation in the type of thromboplastin used often leads to periodic confusion on hospital wards. Each type of thromboplastin has individual characteristics which affect the absolute prothrombin time values obtained (4, 11). Normal values and curves derived by plotting prothrombin time against "percent prothrombin activity" vary with each thromboplastin. Obviously,

then, any change in the thromboplastin used in a laboratory requires *re-establishment of control values* using this thromboplastin. The clinician must consider the possibility of thromboplastin change if prothrombin times issued from a given laboratory suddenly become longer or shorter. The variation in prothrombin times appears related to the amount of factor VII in the thromboplastin used. Preparations devoid of factor VII

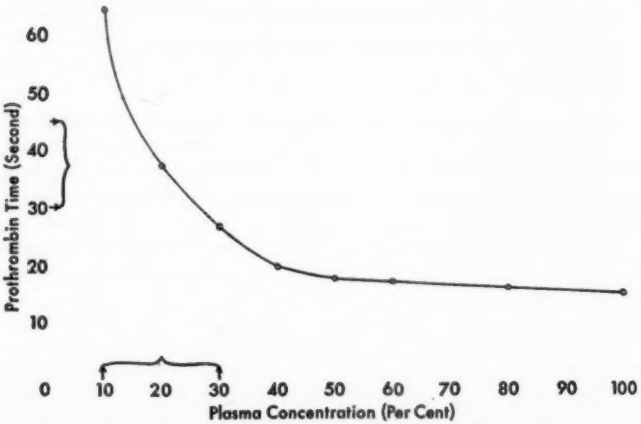

FIG. 1.—Typical prothrombin curve. The characteristics of this curve will vary considerably with changes in technic and with the particular thromboplastin used (see text). Therapeutic ranges of 2–3 times normal (100%) time and 10–30% activity are indicated.

are preferable because they will reflect most accurately the depression of *both prothrombin and factor VII* in the plasma (4, 11).

The methods used for reporting results are also of considerable importance. Reporting as "percent prothrombin activity" is widely practiced. This method depends on reference to a standard curve of the type represented in Figure 1. In the construction of this curve, dilutions of normal plasma (or commercially available "artificial" plasma) are represented on the abscissa as percent normal activity; the ordinate indicates prothrombin times ob-

tained at these various dilutions. Results of clinical prothrombin time determinations are compared with this curve and reported as percent of normal activity. Since this curve varies with different thromboplastins and other factors (11), it should be reconstructed if there are changes in personnel, thromboplastin or technic. In any case, several points on the curve should be checked daily.

Many laboratories report results of the test and the control plasma in seconds rather than percent. This eliminates the need for periodic reconstruction of activity curves. Only a "100%" control—i.e., a time on normal or artificial plasma—need be carried out daily.

As is apparent in Figure 1, the behavior of the prothrombin activity curve is less than ideal for clinical purposes. A few seconds in prothrombin time represent large percentage changes on the flat portion of the curve, while large time changes reflect minimal percentage changes on the steep portion. These characteristics should be borne in mind by those using "% activity" reports alone. For this and the other reasons mentioned above, I prefer reporting in seconds in addition to—or in place of—percentages.

THERAPEUTIC OBJECTIVES, DRUGS AND DOSAGE.—The ability of the PTP drugs to prevent intravascular thrombosis is still subject to some question after two decades of use. Certainly no one regards them as an antithrombotic panacea. Furthermore, even among the great majority which agrees that the drugs have proved effective, much controversy exists regarding the level of clotting factor depression which assures maximum therapeutic effect.

That the PTP drugs do not provide absolute protection against thrombosis is amply confirmed by both clinical and experimental evidence. Thrombotic events do appear in individuals admittedly well controlled on a PTP agent, and clot formation can be induced experimentally in dogs receiving therapeutic doses of bishydroxycoumarin (12). The fact that the *anticoagulant* effect of these drugs cannot be equated directly with *antithrombotic* activity should not be surprising. Reduction of PTC, factor VII and prothrombin does not totally subvert the ability of the coagulation mechanism to achieve fibrin formation.

Despite these necessary qualifications, there is now ample evidence that the agents do prevent thrombosis or limit its consequences in many patients when used properly (13–15). But what standards should we adopt for "proper" dosage? This is a difficult question to answer, since most of the information regarding "adequate" or "therapeutic" dosages is of an indirect nature gleaned from clinical experience. A range of "prothrombin time" prolongation or "percent prothrombin" was empirically adopted by certain groups as a "therapeutic range," and observations were made indicating that maintenance of such ranges was clinically effective. Unfortunately, different groups have "proved" to their satisfaction that *different* levels of prothrombin-complex depression are "effective" clinically. The confusion is compounded by the fact that various methods of performing the prothrombin time have been used to establish these therapeutic ranges (16).

This heritage of confusion obviously makes it impossible to state categorically that one dosage level is wrong and another is right. There are no magic numbers in the matter of *optimal* dosage. There is, however, rather general agreement regarding the limits of *safe* dosage. The incidence of minor and major hemorrhagic events appears to increase rather sharply when the one-stage prothrombin time is prolonged beyond three times normal or the percent activity falls below 10–15%. Unfortunately, the correlation between the development of hemorrhage and the results of the one-stage test or any other test are far from absolute. Some patients will tolerate much greater depressions of prothrombin-complex activity without hemorrhage, while others bleed with subtherapeutic prolongation of the prothrombin time. Nevertheless, it appears unwise to seek levels greater than those cited (about 10–15% activity or 2–3 times normal time), since the statistical risk of bleeding is greater and there is no evidence that better therapeutic effects are achieved.

What constitutes optimal dosage is much less clearly defined. Is a prothrombin time of 3 times normal more effective than one which is twice normal? Is a level of 20% activity more likely to prevent thrombosis than a 30 or 40% level? These questions cannot be answered. Clinical data can be found to support a number of different points of view. The greatest experience in the United States has been obtained with therapeutic programs

which aim for prolongation of the prothrombin time to *at least twice* normal or for depression of activity to 30% or less (17, 18). Dosages of the PTP drugs which achieve these minimum goals have proved effective therapeutically in large groups of patients reported by others as well as in my own experience.

On the basis of the evidence mentioned above, I routinely recommend that a range between 2 and 3 times normal prothrombin time (or 15–30% of normal activity) be maintained during therapy with coumarin or the indandione drugs. This range qualifies as both safe and effective. It would appear advisable to lean toward the lesser figures (2 times or 30%), since these levels are probably equally as effective and less dangerous.

Having set these goals, we should next consider the particular drugs available to achieve them. A large number of PTP drugs are now available. Each has a characteristic onset and duration of action, initial and maintenance dosage, etc. The cardinal rule in the use of these agents is that the physician *become fully familiar with the use of at least one of them* and adopt it as his standard "drug of choice." Frequent switching from one preparation to another is likely to promote confusion and improper use.

Bishydroxycoumarin (Dicumarol), the first PTP drug synthesized, probably is still the most widely used. However, it is far from ideal in many respects. The major shortcomings of bishydroxycoumarin are: (1) its inconstant degree and speed of *absorption* from the gastrointestinal tract; (2) its delayed and variable *onset* of action; (3) the limitation of administration to the *oral* route; and (4) the rather *slow return* of coagulation components to normal after the drug is discontinued. All of the drugs introduced since bishydroxycoumarin represent attempts to overcome one or more of these clinical disadvantages. However, bishydroxycoumarin merits detailed consideration here because it is the prototype of the PTP agents and its actions have been studied extensively.

In most instances, the therapeutic range mentioned previously can be achieved by a dosage schedule consisting of 250–300 mg. on day one, 100–200 mg. the second day (depending on response of the prothrombin time) and 25–100 mg. per day thereafter as a maintenance dose. In initiating therapy with this drug, one

should realize that the full effect of a dose given may not appear for 48–96 hours. Failure to appreciate this lag period may lead to overdosage. For example, a large (300 mg.) dose should not be repeated on day two because minimal prothrombin time prolongation has occurred at that time. Uncertainty due to this lag phase and the variability of both absorption and individual response make initiation of therapy somewhat of a trial-and-error procedure in each patient. It is preferable to err on the side of lower dosage if question exists. In this connection, one should be alert to certain individuals who are especially sensitive to PTP agents: patients with liver disease, severe congestive heart failure, renal insufficiency and severe debility or cachexia. In such subjects, it is well to begin at the lower dosage levels. Maintenance therapy with bishydroxycoumarin requires close observation. Often a stable daily dose cannot be established and one must use a schedule such as 50 mg. one day and 25 mg. the next for good control. When therapy is discontinued, the anticoagulant effect of bishydroxycoumarin persists for some 48–96 hours. If more rapid interruption is desired, fresh blood or vitamin K_1 should be administered (see below).

Each of the other PTP agents in current use varies in several respects from bishydroxycoumarin. *Ethyl biscoumacetate* (Tromexan) is approximately one fifth as active, milligram for milligram. Initial dosage therefore ranges from 1,000 to 1,500 mg., usually administered in two or more doses during the day. Its major advantages include rapid and complete *absorption* leading to more prompt achievement of therapeutic levels, usually within 24–36 hours; rapid *excretion* with loss of anticoagulant activity within 36–48 hours after cessation. Unfortunately, the drug is rather erratic in action and difficult to use in maintenance therapy. Therefore, its major area of use has been in the *initiation* of anticoagulant therapy after which a more predictably active drug is substituted. Another widely used agent is the indandione drug *phenindione* (Hedulin). This agent is also rapidly and completely absorbed after oral administration. The therapeutic range is achieved within 24–48 hours. Its anticoagulant effect also ceases more promptly than bishydroxycoumarin. Phenindione is usually administered twice a day with total dosage being slightly higher than required with bishydroxycoumarin (e.g.,

300–400 mg. or more initial dose). In my experience the drug has been satisfactory for both initiation and maintenance of therapy.

In the last several years, another coumarin derivative has gained great popularity. Indeed, it approximates the ideal prothrombinopenic agent closely enough to be regarded by many, including myself, as the PTP drug of choice. This agent is *warfarin* (Coumadin), developed in the same laboratory which first synthesized bishydroxycoumarin—that of Professor Paul Link (19). Warfarin is rapidly and completely absorbed. Therapeutic response of the prothrombin time regularly occurs within 24–36 hours. Warfarin is the only generally available PTP agent which also can be administered intramuscularly and intravenously. Dosage by all routes is virtually the same. This ability to interchange the oral and parenteral routes is an obvious advantage. In my experience, therapy with warfarin has been quite easy to initiate and maintain. After an initial dose of 60–75 mg. and a second-day dose of 15–20 mg., a maintenance schedule of 2.5–10 mg. per day is usually adequate. The anticoagulant effect of the drug disappears within 36–48 hours after cessation of therapy.

Because of its advantages, warfarin will likely displace the older PTP drugs (19). However, any of the PTP agents available can yield satisfactory therapeutic results if used with adequate knowledge of their particular characteristics and with clarity of purpose in regard to the prothrombin time prolongation desired.

Heparin

As in the case of bishydroxycoumarin, serendipity played a major role in the discovery of heparin. The observations of a medical student attempting to define accelerators involved in coagulation set in motion the chain of events which led to the establishment of heparin as an effective antithrombotic agent (20). This transition from observation to application was a slow and difficult one, spanning some 20 years of study by many investigators. Indeed, even at the present time, the last chapter of this story has not been written. We still have much to learn about the functions and composition of heparin.

The relative ease with which the coumarin drugs were isolated

and synthesized reflected the comparatively simple chemical structure of these compounds. Unfortunately, heparin bears little resemblance to its therapeutic allies in this respect. The complex chemical characteristics of heparin have made this agent resistant to synthesis thus far and make it unlikely that synthesis will be accomplished in the near future. All preparations of heparin currently available are derived by extraction from animal tissues known to be rich in this material, a tedious and expensive process.*

It is not surprising that attempts to isolate pure heparin or to duplicate it in the laboratory have proved most difficult, for heparin has peculiar physicochemical properties. It is a complex mucopolysaccharide which is, to quote Jorpes, "esterified with sulfuric acid to a quite extraordinary degree" (21). Compounds of this type do not lend themselves to crystallization, a fact which greatly hinders detailed study of their molecular structure. While many of the components and linkages of heparin are now known, important details of its configuration are still lacking.

The extremely high content of sulfuric acid confers on heparin two characteristics which render it unique among the active constituents of body chemistry—namely, it is the strongest organic acid found in man and it possesses a very strong electronegative charge. Undoubtedly these two unusual properties play an important role in the anticoagulant activity of heparin.

MECHANISM OF ACTION.—Coagulation is essentially a series of complex chemical reactions proceeding toward the ultimate production of fibrin. A multiplicity of substrates and enzymes, referred to as coagulation factors, participate in these reactions. Since each phase of coagulation is dependent to some extent on proper completion of the prior stages, interference at any point will have an effect on fibrin production. Depending on the degree to which these essential reactions are impaired, the appearance of fibrin may either be *prevented entirely* or be *diminished* so that fibrinolytic mechanisms can deal with the fibrin produced.

In this age of "the missile," a ready simile is supplied by considering the multistage space rockets. In these complex electronic

*While heparin owes its name to the fact that the liver was the original source and contains the highest content of the material, the lung has since proved a less expensive and quite satisfactory source.

devices, malfunction of one component may result in either *total failure* or in various degrees of partial failure. Complete success of the missile depends on smooth functioning of all electronic components in each stage. Carrying the simile further, we can emphasize the differences between the anticoagulant actions of the PTP drugs and heparin. The former interfere with coagulation by *reducing* or *eliminating* certain important components involved in this delicately balanced process. Heparin, on the other hand, *inhibits* various critical reactions involved in coagulation without altering the plasma content of the components themselves. It is likely that heparin exerts these inhibitory effects by blocking the action of various enzymes (coagulation factors) through the effects of its strong electronegative charge, much as electrical interference can disrupt the function of our electronic simile, the space rocket.

The sabotage created in the coagulation mechanism by heparin is quite widespread. It impairs the ability of platelets to aggultinate, rendering them less sticky. It interferes with the *action* of thromboplastin on prothrombin. It impedes the *conversion* of prothrombin to thrombin even in the presence of excessive thromboplastin. Finally, heparin compromises the ability of thrombin to convert fibrinogen to fibrin. Thus, heparin is at once an antiplatelet, antithromboplastin, antiprothrombin and antithrombin. The clotting factors remain intact, but their functions are frustrated at every turn by heparin.

Clotting time determination.—The clotting time of whole blood is used almost universally to measure the in vivo effect of heparin. This simple test reflects the extent to which fibrin formation is impaired without implication as to why such impairment occurs. Like prothrombin time values, clotting times are meaningless unless one is familiar with the methods being used. I am frequently asked whether a clotting time of 15 minutes is satisfactory—or whether one of 25 minutes is dangerous. Such questions often cannot be answered because the questioner does not know *who did the test, when* it was done in relation to heparin administration, *what method* was utilized or what the pre-treatment *control* values were. If clotting times are to be used as a guide to heparin therapy, we must have all these data. Furthermore, we must be familiar with the factors which alter the

absolute times obtained. These include: the size of the test tubes used; whether the tubes are siliconized, wet or dry; whether the procedure is carried out in a water bath or at room temperature; and how frequently and to what extent the tubes are disturbed during the test. Actually, *it does not matter which variation of the clotting test is employed as long as the factors mentioned are clearly recognized and kept as constant as possible.* On the other hand, it is preferable to omit clotting times rather than to rely upon improperly performed or unstandardized tests.

The most frequently used clotting time method is that described by Lee and White (22) or some minor modification of this procedure. I have found the Lee-White procedure quite satisfactory for routine use. It is rapid, simple to perform and requires no special apparatus. Methods employing siliconed glassware are also satisfactory, but the clotting times obtained are longer. I have not found the use of "capillary" tube clotting times either as reproducible or as reliable as the other methods, although this method has the obvious advantage of avoiding repeated venipuncture.

AIMS OF THERAPY AND DOSAGE REGIMENS.—The objectives of heparin administration are the same as those mentioned in connection with the PTP drugs. First, we desire *maximum protection* against onset or extension of thromboembolism. Second, we want a program which is *safe*. Finally, we would like a dosage schedule which is *practical* for routine clinical use. While the clotting time is widely accepted as the best therapeutic guide to heparin administration, there is little agreement as to the clotting time changes which should be sought in accordance with these objectives.

Much of the debate regarding heparin regimens centers about the important question: "Is constant prolongation of the clotting time more effective than intermittent prolongation?" Some workers hold the former view, while others are equally convinced that a program which gives peaks and valleys in the clotting time is just as effective. Review of the literature and my personal experience indicates that either method appears to achieve the objectives mentioned above. Since there is no clinical or experimental evidence which clearly indicates that one method is supe-

rior to the other, choice must be based on a blending of practical considerations, personal experience and theoretical preference.

Even the *limits of safety* in terms of clotting time prolongation are not clearly defined. In general, we avoid extended prolongations greater than 3 times the baseline value, since the risk of hemorrhage at this level or below is quite small. However, experience has indicated that heparin is an extremely safe anticoagulant even when this arbitrary upper limit is exceeded by a wide margin for brief periods. Indeed, with some standard intermittent dosage regimens, marked prolongations are the rule during the period of maximum heparin effect and are invariably tolerated without difficulty. However, since it is unlikely that more effective anticoagulant action is achieved by prolonged maintenance of a clotting time greater than 3 times normal, this value serves as an acceptable upper limit.

The *lowest level* of dosage compatible with therapeutic effect is even more difficult to establish. When heparin is administered intermittently, the clotting time often is permitted to return virtually to normal before the next dose. Other regimens constantly maintain the clotting time at least twice the normal value. The definition of effective dose is therefore conditioned chiefly by one's preference for intermittent or continuous therapy.

Finally, it should be recognized that many physicians do not employ clotting determinations as a guide to heparin therapy. They administer doses which they have found safe and effective on the basis of experience, and they regard routine clotting times as unnecessary.

From the statements made thus far, it is apparent that there is no standard heparin dosage schedule. Many different regimens are employed in various parts of the world—apparently with equal success. I shall review here only a few of the most popular dosage schedules.

Continuous intravenous drip.—In this technic, 150–200 mg. of heparin is placed in 500–1,000 cc. of intravenous fluid. Continuous intravenous administration is regulated according to the results of clotting time determinations performed at 3- to 4-hour intervals. Usually the clotting time is maintained between 2 and 3 times normal. While undoubtedly highly effective, this method

is rather cumbersome for clinical use, especially if heparin therapy is to be continued for any length of time.

Intermittent intravenous injection.—This method, still popular in several centers, involves periodic intravenous administration of heparin (23). To avoid repeated venipuncture, an indwelling needle or plastic catheter is often used. The intervals between injections depend on the dosage employed and whether one desires to achieve a steady or picket fence type of clotting time response.

One popular method utilizes doses of 40–60 mg. at 4-hour intervals throughout the day. Other workers use larger, less frequent doses. It is important to recognize that the larger the dose of heparin, the greater will be the *duration* as well as the *intensity* of effect on the clotting time (24). For example, a dose of 50 mg. intravenously will usually prolong the clotting time for 2–3 hours, while 100 mg. will maintain an effect for 5–6 hours. A greater maximum prolongation of clotting time also follows the latter dose. In the Scandinavian countries especially, the intermittent intravenous use of large doses (100–150 mg.) of heparin at 6- to 8-hour intervals is quite popular, and usually no clotting time checks are carried out (25).

Intramuscular and subcutaneous administration.—Since highly concentrated solutions of aqueous heparin have become available, intermittent subcutaneous and intramuscular administration have become the most popular technics of heparinization. Because intramuscular injection usually is attended by formation of significant hematomas, the subcutaneous route is generally preferred. Injection can be made subcutaneously in various sites on the extremities and the abdomen. Fatty areas are preferred. Hematoma formation may occur but is usually minimal and rarely interferes with the maintenance of therapy. As with intravenous therapy, one can choose between smaller, more frequent or larger, more widely spaced doses. The regimens most commonly used are 75 mg. every 6 hours, 100 mg. every 8 hours or 150–200 mg. every 12 hours. Single large daily injections also have been used but have been less predictable and satisfactory in my experience.

My own program for heparinization is as follows: After a baseline clotting time has been obtained, 50 mg. of heparin is administered intravenously to achieve immediate anticoagulant

effect. Simultaneously, the patient is begun on 75 mg. subcutaneously at 6-hour intervals. Clotting times are performed 3 hours after the second dose and just prior to the third dose. The former reflects peak effect and should be 2–3 times the pretreatment value. The latter should be descending toward normal as a guarantee against cumulative effect. Dosage is adjusted accordingly. If either value is borderline, it is replaced after the next dose. On the second day of therapy, clotting times are again performed at the intervals indicated. If the results are satisfactory, the dosage is thereafter maintained without further check of the clotting time. If therapy is maintained for long periods, I frequently shift to dosage schedules of 100 mg. every 8 hours or 150 mg. every 12 hours to reduce the total number of injections. Clotting times are rechecked when the dosage schedule is altered—again midway between doses and prior to the next dose.

Whether any clotting times are actually necessary for adequate management with subcutaneous (or any form of) heparin is questionable. When accurate determinations are available, I prefer to obtain them as indicated above. However, if clotting times are not reliably performed or if repeated venipuncture poses a problem, I do not hesitate to carry out heparinization without them.

Each of the dosage regimens described is acceptable for general use. In practice, choice is often dictated by local factors. For example, intravenous therapy is more popular in centers which permit nursing personnel to administer drugs intravenously or where larger house staffs are on duty. Obviously, if intravenous injections can be given only by a physician who may not be readily available, subcutaneous injections will provide more reliable protection for the patient.

The Fibrinolytic Agents

The therapeutic challenge posed by the thromboembolic disorders has not been met completely by the PTP drugs and heparin. The anticoagulant drugs offer protection against both the *development* of thrombosis and its *extension*. However, they exert little effect on *intravascular clot which is present when anticoagulant therapy is begun*. Since this *original* thrombus is often

the major cause of morbidity and mortality, ideal antithrombotic therapy should include some method for prompt removal of the existing clot. Until recently, no medical method for rapidly achieving clot removal was available. Unless surgery were feasible, restoration of the blood flow was dependent on the activity of intrinsic body mechanisms for dissolving or recanalizing thrombi. Unfortunately, such mechanisms often function too slowly or inadequately to prevent tissue damage after acute arterial or venous occlusion.

During the past several years, considerable progress has been made toward the development of agents which may be effective in promoting rapid dissolution of intravascular clot. One such agent is already available for clinical use, and others will undoubtedly become available shortly. It therefore behooves the physician to become familiar with these new agents. Such familiarity is essential to proper use of the available drugs and will provide criteria for evaluation of future developments in this rapidly moving field.

MECHANISM OF ACTION.—The concept of fibrinolysis is not a new one. Since the turn of the century, it has been known that mammalian blood possesses some intrinsic mechanism for dissolving clot. Furthermore, since the protein fibrin was known to provide the framework of blood clot, it was apparent that clot dissolution was actually a manifestation of fibrin dissolution—i.e., fibrinolysis. However, the substances responsible for fibrinolysis remained obscure for many years. In 1933, Tillett and his associates noted that filtrates from cultures of the beta hemolytic streptococcus contained a substance which induced rapid dissolution of fibrin. Discovery of this material, now widely known as streptokinase, renewed general interest in fibrinolysis, and knowledge of the mechanisms involved in fibrin dissolution rapidly expanded.

It is now known that mammalian plasmas contain an enzymatic system capable of dissolving fibrin. This intrinsic fibrinolytic mechanism appears to serve a homeostatic function by maintaining the organism free of unwanted fibrin deposits (26). The major components of this mechanism are indicated in Figure 2. An inactive precursor substance, *pro-fibrinolysin* (plasminogen) can be converted by a number of *activators* to an active proteo-

lytic enzyme, *fibrinolysin* (plasmin). Fibrinolysin, once elaborated, is subject to the influence of at least two plasma inhibitors.

Pro-fibrinolysin (pro-F) resides in the euglobulin fraction of human plasma proteins. Its electrophoretic mobility resembles that of the beta globulins. By combining modern protein fractionation technics with chemical purification procedures, pro-F can be obtained in highly purified form from the plasma. When this material is administered to animals or man, it has no apparent effect. Humans tolerate large doses intravenously with no

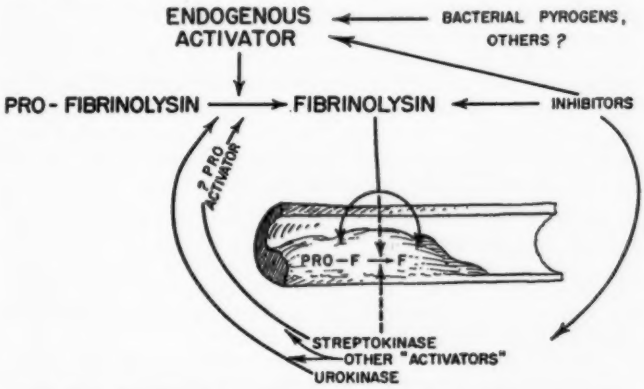

FIG. 2.—Diagrammatic representation of the fibrinolytic mechanism.

detectable toxicity or alteration in plasma fibrinolytic activity (27). One especially important characteristic of pro-F is its adsorptive affinity for fibrin (28, 29). As we shall indicate below, this affinity between fibrin and pro-F (and fibrinolysin) has significant therapeutic implications.

Conversion of pro-F to fibrinolysin is accomplished in vivo by an endogenous activator which has not yet been isolated. In vitro, this conversion is readily achieved by a variety of "artificial" activators, including chloroform, trypsin, streptokinase (SK), urokinase (UK) and staphylokinase. Slow, spontaneous activation also occurs in vitro. The conversion of endogenous pro-F to

fibrinolysin in vivo can also be promoted by intravenous administration of SK, SK-pro-F mixtures, UK, certain bacterial pyrogens, and nicotinic acid. The end-product of pro-F activation, fibrinolysin, is a proteolytic enzyme. It is capable of destroying a wide variety of proteins both in vivo and in vitro under appropriate conditions. However its "preferential substrate" is fibrin (30). While there are probably multiple reasons for its fibrin preference, the mentioned adsorptive affinity of fibrin for fibrinolysin undoubtedly plays a major role.

APPROACHES TO THERAPEUTIC FIBRINOLYSIS.—It is apparent from Figure 2 that there are four possible methods for enhancing fibrinolytic activity in vivo to promote clot lysis: (1) administration of activators of *endogenous* pro-F; (2) administration of fibrinolysin itself; (3) reduction of the fibrinolysin inhibitors; or (4) combinations of these three approaches. Thus far, therapeutic efforts have involved only the use of activators, fibrinolysin itself or fibrinolysin-activator combinations. There are proponents of each approach. Sufficient experience has not been accumulated to clearly establish which method is most efficacious and practical. At the moment, the problem is an academic one for the practicing physician, since only one preparation (a fibrinolysin-activator combination) is available for clinical use. Nevertheless, for purposes of guidance in this new field, certain comments in this regard are warranted here.

Activators.—The only activator presently suitable for use in man is *streptokinase* (SK). This substance is now available in highly purified form. However, all preparations of SK available retain some temperature-elevating activity and antigenic risk. The events which follow intravenous administration of SK to man have been studied extensively by various investigators (31–33). The fibrinolytic effect of SK is *totally dependent* on the content of pro-F in the plasma and in the clot itself; if plasminogen has been depleted (by prior infusion of SK or any other mechanism), clot lysis cannot be obtained with SK administration. Furthermore, because of the prevalence of streptococcal infections, a significant proportion of the general population has antibodies against SK (34, 35). This invokes the need for antibody measurement in individuals who are to receive the drug if adequate activation of pro-F is to be achieved. However, when sufficient

quantities of SK are administered, it is a potent pro-F activator and can promote rapid clot dissolution in both experimental animals and man (36).

Urokinase (UK), obtained from mammalian urine, is a potent activator of pro-F, but it has not yet been sufficiently purified for general clinical trial. This material has considerable promise, since it does not appear to share the antibody limitations of SK.

Certain *bacterial pyrogens,* lipopolysaccharide extracts of gram-negative bacteria, will activate pro-F when administered intravenously to man (37). Apparently they act by releasing an endogenous activator, since they will not activate plasminogen in vitro. Their activator function is not impaired when temperature elevation is blocked by antipyretics. There is some objection to the use of these agents in man because similar extracts from gram-negative bacteria have been implicated in the production of irreversible shock and other disorders. Repetitive use might prove especially hazardous. Furthermore, pyrogenic compounds have effects on cardiopulmonary function which occur even in the absence of temperature elevation (38). Despite such objections, these interesting activators are deserving of further study.

Nicotinic acid, another entrant in the activator field, is a moderately good pro-F activator, according to most reports (39). It apparently loses its activator effect when used repetitively. Nevertheless, it also merits further evaluation, for, from the toxicity standpoint, it is the least objectionable activator thus far uncovered.

A mixture of SK with pro-F, in addition to producing fibrinolysin, forms an intermediary substance with activator function (see below).

Undoubtedly, other activators of pro-F will shortly be discovered. In my opinion, all will be subject to the same basic objection—namely, their total dependence on endogenous plasminogen for their fibrinolytic effect. Overdosage may lead to both excessive release of fibrinolysin and depletion of endogenous pro-F. The former effect would lead to destruction of other coagulation factors; the latter would render the agent ineffective if rethrombosis should appear promptly. While these problems may be overcome by proper dosage regulation, they presently constitute

major objections to complete reliance on any activator as a clot dissolvant for clinical use.

Fibrinolysin and fibrinolysin-activator combinations.—Preparation of fibrinolysin itself involves the *isolation* of pro-F from the plasma and its *activation. The particular properties of the fibrinolysin ultimately obtained are dependent on the exact methods used in these two steps.* To illustrate this important principle, I shall first consider the isolation of pro-fibrinolysin.

All preparations of pro-F are obtained by procedures which concentrate the euglobulin fraction known to contain lytic activity. The extent to which this concentration is carried has both technical and practical limitations. Each additional purification procedure involves a loss in total yield; i. e., less protein with lytic activity is obtained from a given amount of plasma. The desire for "pure" material is tempered somewhat by this consideration. Therefore, virtually all pro-F actually is pro-F *plus* a variable amount of other globulins. The actual pro-F content in this mixture can be determined only by testing the fibrinolytic activity present after activation—not by weight considerations. Accordingly, we must speak of the *fibrinolytic activity* of a preparation as determined by *some specific test* until such time as crystalline pro-F is available.

As indicated above, the second step in fibrinolysin preparation, *activation* of pro-F, can be achieved by numerous methods. Spontaneous activation, trypsin, SK and UK—all can accomplish this conversion. The characteristics of the end-product obtained are not uniform. They are influenced by the particular activator used, the proportions of the activator-pro-F mixture, the specific conditions of activation and the type of pro-F used. Each variation in the method of activation produces different fibrinolysins. For example, mixtures of SK and pro-F do not result in the single end-product of fibrinolysin. Two materials actually result: (1) a intermediary combination of SK and pro-F which itself is an *activator* of pro-F with characteristics different from SK; (2) the proteolytic enzyme fibrinolysin per se. By varying the amounts of SK and pro-F mixed and the conditions in effect during activation, one may obtain products which are pure proteolytic enzyme, pure activator or various mixtures of the two.

FIBRINOLYTIC UNITS.—A unit is an indirect measurement based

on some specific activity of the substance in question. Expression in units usually implies that it is impossible or impractical to measure the substance in a pure or crystalline state as milligrams or cubic centimeters. *Any "unit" derives its significance from the test on which it is based.* For example, an alkaline phosphatase of "5 units" cannot be evaluated properly unless it is known whether these are Bodansky or King-Armstrong units. Fibrinolytic units are no exception to the rule. They are measures of *activity* and can be interpreted adequately *only if the conditions under which they are determined are known.* Each of the several types of fibrinolysin currently under study is labeled as containing a certain number of "fibrinolytic units." These units do not have the same meaning from one preparation to another, since each unit (Loomis, Christensen, etc.) is based on a *different assay method* (27, 40–42). Obviously, such units cannot be used interchangeably. As has been the case with many drugs now in common use, the fibrinolytic unit confusion will ultimately be resolved. Until then, the physician must be alert to the situation, especially since fibrinolysins *based on different unit systems* may soon be available.

CHOICE OF AGENT, DOSAGE AND TOXICITY.—At the moment, only one preparation of fibrinolysin has been released for general clinical use. This material, Actase,* consists of human pro-F activated with SK. It is lyophilized after activation to a highly soluble white powder and is administered intravenously after dissolution in any standard form of intravenous fluid. The final material has both activator and enzyme action. The fibrinolytic unit defined for this agent is based on its ability to dissolve a "standard clot" formed of bovine fibrinogen and human thrombin (27).

Neither the minimal dose effective in achieving thrombolysis nor the upper limits in terms of safety have been firmly established. My experience has suggested that a rough guide to adequate dosage is supplied by serial measurements of plasma fibrinolytic activity—i.e., the ability of the patient's plasma to dissolve a standard fibrinogen-thrombin clot in vitro (43). Doses which lead to a detectable increase in plasma fibrinolytic activity appear to be effective clinically. This dosage has averaged 100,-

*Actase-fibrinolipin (human), Ortho Pharmaceutical Corp., Raritan, N.J.

000 fibrinolytic units (as defined above) given over a 3-hour period in the patients studied to date but has ranged from 30,000 to 150,000 units or more in individual cases (44). While it may not be necessary to give doses of sufficient size to increase plasma fibrinolytic activity, I currently use this arbitrary criterion to judge whether an effective dose has been administered. In view of the long-term controversy regarding effective doses of heparin and the PTP drugs, it is not likely that the problem of adequate dosage with Actase and similar compounds will be settled quickly.

The question of maximum safe dose may be easier to answer. Studies of the coagulation changes which follow administration of fibrinolysin have indicated that it will actively attack some coagulation factors despite its adsorptive affinity for fibrin. As might be expected because of its similarity to fibrin, fibrinogen is the factor most affected by fibrinolysin in vivo. Fibrinogen depletion, therefore, would appear to be the ultimate limiting factor in dosage. Obviously, the *intervals* of administration will play as important a role as the *total dose* given at any one time. Doses as high as 400,000 fibrinolytic units of the commercial material have been administered over a 2-hour period to humans without hemorrhagic complications (45). Whether larger doses, which might significantly deplete fibrinogen, may be necessary to achieve clot lysis in some situations is presently unknown.

The toxicity of Actase has been largely limited to temperature elevation. An elevation of 1° F. or more above base-line temperature occurs in some 50% of the patients who receive the drug without prophylaxis. Elevations of 4° F. or more have been observed in 5%. Other fibrinolysin preparations have shown a similar incidence and degree of pyrogenicity. We routinely administer antihistaminics, barbiturates and/or aspirin to reduce the incidence and intensity of febrile response. Allergic reactions have occurred in less than 1% of patients treated with the commercial agent. Most of the reactions have consisted of local urticaria at the infusion site, but one instance of generalized urticaria and one of classic serum sickness have been observed. No anaphylactic-type reactions have occurred.

One toxic reaction to this fibrinolysin preparation is worthy of

special mention—namely, severe upper epigastric pain which appears during or shortly after the infusion. Extensive study in several patients has failed to define its cause. The syndrome responds promptly to opiates and apparently leaves no detectable residuals. While this syndrome has been observed in only 6 patients to date, physicians should be alert to its possible development, since it is a rather dramatic event despite its apparent benignity and requires etiologic definition.

REQUIREMENTS FOR SUCCESSFUL THROMBOLYSIS.—While the fibrinolytic agents are still in an early phase of development, the major factors determining successful clot dissolution are already rather clear (Table 2). These factors should be recognized by all physicians who contemplate the use of fibrinolytic therapy.

TABLE 2.—REQUIREMENTS FOR SUCCESSFUL THROMBOLYSIS WITH FIBRINOLYTIC AGENTS

1. Correct diagnosis of thrombosis
2. Adequate fibrinolytic dosage regimen
3. Favorable structural properties of thrombus
4. Concomitant use of anticoagulant drugs to prevent thrombosis

Correct diagnosis.—No clot-dissolving agent will help a patient whose "thrombophlebitis" is actually cellulitis or whose artery is occluded by an atheromatous plaque. Therefore, every attempt should be made to assure diagnostic accuracy. However, until better diagnostic methods are available to identify the presence of thrombus (particularly in arterial occlusive events), a certain number of patients with nonthrombotic occlusion will be treated unsuccessfully with fibrinolytic agents. We must be prepared to accept this and must bear in mind that failure to restore blood flow may reflect nonthrombotic etiology rather than true drug failure.

Adequate dosage.—I have indicated that we have only preliminary information regarding proper dosage regimens. As new data and different preparations appear, criteria of adequate dosage may alter considerably. Furthermore, I believe that *different thrombotic processes will have different dosage requirements*—much as antibiotic dosage varies in infectious processes.

For example, we currently believe that 100,000 fibrinolytic units of Actase is a satisfactory initial dose in acute deep thrombophlebitis, while acute peripheral arterial occlusion appears to require larger, more frequent doses (see below). In coronary and cerebral thrombosis, where time will be a critical factor, even larger and more frequent doses may prove necessary.

Age of thrombus.—A clot is a dynamic, changing entity. The fibrinolytic agents can dissolve only *fibrin clots exposed to circulating blood.* No agent can be expected to dissolve a thrombus once extensive organization or endothelialization has occurred. How long a fibrin clot remains subject to dissolution is presently unknown. Estimates range from 3 to perhaps as long as 7 days, depending on location, extent of coexistent inflammation, etc. (46). Furthermore, a thrombus in a given patient may contain areas of different age, so that *partial* dissolution may be achieved. What seems clearly established is that *the more recent the clot, the more susceptible it is to fibrinolytic attack.* Early diagnosis and therapy assumes great importance if therapeutic failure due to changes in clot structure is to be avoided.

Anticoagulant therapy.—Fibrinolytic agents are not anticoagulants, although new clots formed in their presence will dissolve promptly. After fibrinolytic activity has disappeared from the blood, however, *the patient is no longer protected against thrombosis.*

It is known that thrombosis will recur in a significant proportion of animals after fibrinolytic dissolution. This dissolution-reformation sequence also has been demonstrated in man (36). Therefore, fibrinolytic therapy has been combined with heparin to prevent rethrombosis. The two types of agents can be used quite safely together because their mechanisms of action differ.

METHOD OF ADMINISTRATION.—Current fibrinolytic agents are effective only by the intravenous or intra-arterial routes. I prefer the use of prolonged infusion rather than a single rapid injection, since a sustained level of fibrinolytic activity may be of some importance. Approximately 30,000–40,000 units per hour are given by constant intravenous drip. However, direct, rapid intra-arterial or intravenous injection has been used with success in special situations.

THERAPEUTIC INDICATIONS FOR THE ANTITHROMBOTIC DRUGS

The three types of antithrombotic drug under discussion have been used in virtually every form of thromboembolic disease. In this section, I shall review only a few of these conditions. Great controversy attaches to their effectiveness in certain instances, while their value in other situations is generally accepted. The following comments represent only one point of view regarding antithrombotic therapy in these disorders.

Myocardial Infarction

Currently I recommend that all patients with myocardial infarction receive anticoagulant drugs unless contraindications exist. The four major objectives of anticoagulant therapy in this situation are: (1) limitation of the extent of coronary thrombosis, (2) prevention of mural thrombosis and its embolic sequelae, (3) prevention of peripheral thrombotic complications (especially venous thrombosis) during the period of bed rest and (4) prevention of recurrent coronary thrombosis. The first three objectives depend on short-term use of anticoagulant therapy; the fourth, on long-term.

Several decisions face the physician who contemplates anticoagulant treatment in myocardial infarction. First, the *"good risk" versus "poor risk"* question arises; that is: Should only the latter type patient receive these drugs? (47, 48). While there is statistical question of their value in good-risk subjects, I indorse their use in all patients, since the patient who is good risk when first seen may become a poor risk unpredictably any time thereafter, and even the good-risk patient is exposed to mural and peripheral thrombosis.

The second decision involves the *choice of anticoagulant drug.* Should heparin be used until the patient has come "in range" with the PTP agents; or should the latter be used alone? Support exists for both courses. I prefer to achieve full anticoagulant effect promptly with heparin. While it already may be too late to prevent mural thrombosis or extension of coronary thrombosis

when the patient is first seen, any chance of achieving these goals is not improved by waiting for the PTP drugs to take effect. Therefore, I begin heparin therapy immediately and administer a PTP agent simultaneously. Heparin is continued until the prothrombin time has reached the desired range. When facilities are not available for prothrombin time determinations, I use heparin as maintenance therapy despite the expense and injections involved.

The next problem is *when to discontinue* anticoagulant therapy. I advocate continuation of therapy until the patient has been fully ambulatory for at least 1 week. Depending on one's criteria for the duration of bed (or chair) rest, this usually implies a 4- to 8-week course. Beyond this period, it is my policy to maintain long-term use of PTP drugs whenever feasible in terms of patient reliability and the availability of laboratory facilities.

In long-term therapy, I seek a lesser prolongation of prothrombin time than that in short-term therapy. In the latter, my goal is 2½–3 times the control; in the former, approximately 2 times. While this change is arbitrary, the propriety of any range is sufficiently nebulous that I prefer to err on the side of "hemorrhagic safety" in long-term situations. Since a change in drug responsiveness often occurs when patients leave the hospital and change their activity pattern, prothrombin time values should be obtained at least twice weekly during the early phases of outpatient therapy. Tests at 1- to 2-week intervals suffice when the patient's dosage requirement has stabilized.

At the present time, the fibrinolytic agents have no place in the standard treatment of myocardial infarction. While experimental results have been encouraging (49, 50) extensive investigation is required before their value can be determined. However, it should be recognized even at this stage that perhaps 50% of coronary occlusions result from subintimal hemorrhage or rupture and embolization of an atheromatous plaque rather than from thrombosis per se (51). No fibrinolytic agent will restore the patency of a coronary vessel occluded by the former mechanisms. Furthermore, even with *thrombosis* the duration of myocardial ischemia before therapy will play a critical role in the ultimate functional results.

I do not use anticoagulant therapy routinely in superficial thrombophlebitis. Local measures (rest, elevation, heat) are tried first. Only if the process extends rapidly after such measures have been instituted do I consider anticoagulant drugs. Usually a 24- to 48-hour period of observation is warranted. Prior history of embolic disease or other special circumstances may influence one to use antithrombotic therapy.

Heparin is my anticoagulant of choice in superficial thrombophlebitis, because of its speed of action and my belief that its anti-clotting activity is superior to that of the PTP drugs. Fibrinolytic agents are also effective in acute superficial thrombophlebitis. They appear to exert both anti-inflammatory and clot-dissolving activity. Like heparin, however, they should be used only if the expense and possible side-reactions incurred by their use seem justified. Anti-inflammatory agents such as intramuscular trypsin or SK and oral phenylbutazone appear to have a place in the management of superficial phlebitis (52, 53, 54). My experience with buccal and oral trypsin and buccal SK has not been satisfactory, and I do not recommend their use.

Acute deep thrombophlebitis calls for different action because of the much greater threat of mortality and morbidity. I believe that all patients with acute deep thrombophlebitis should receive anti-thrombotic therapy. While others do not concur (23), I believe that the situation is analogous to the "good risk" versus "poor risk" distinction in myocardial infarction in which original impressions may subsequently prove erroneous.

General agreement exists as to the advisability of bed rest and leg elevation during the period of acute phlebitic symptoms (systemic temperature elevation, and heat, redness, turgidity and tenderness of the extremity). Local application of heat and the use of elastic bandages are also widely endorsed. Beyond these basic maneuvers, a variety of therapeutic choices are available.

"Standard" therapy includes the use of heparin and/or the PTP drugs. I favor the immediate administration of 50 mg. of aqueous heparin intravenously and 75 mg. subcutaneously. The patient is then maintained on a subcutaneous heparin regimen of approximately 300 mg. per day in two, three or four divided

doses. The patient is ambulated 24–48 hours after all evidence of acute phlebitic activity (see above) has subsided. Slight residual edema or discrepancy in leg size are not regarded as contraindications to ambulation. The patient is maintained on heparin during the first 24 hours of ambulation, and the drug is tapered over the next 24–36 hours. After a full day of ambulation without heparin therapy the patient is discharged. Elastic stockings are worn for 3–6 months. I have found this protocol to be highly successful, and it has been attended by a low incidence of embolic and other complications.

Other regimens, which differ from that just described, are also widely employed. Frequently the patient is begun on heparin and a coumarin drug simultaneously, heparin being discontinued when the prothrombin time has reached therapeutic range. Other physicians use PTP drugs alone. There are no authoritative data indicating that one regimen is superior to the others. Many physicians also use arbitrary limits for the discontinuance of bed rest and anticoagulant therapy—e.g., 10 days of bed rest or 2 weeks of anticoagulant drug administration. While I prefer to base such decisions on the subsidence of phlebitic activity, I cannot quarrel seriously with those who advocate other criteria.

I recommend extended anticoagulant therapy if a patient has had prior episodes of deep thrombophlebitis or suffers a recurrence soon after anticoagulant therapy is discontinued. Treatment is arbitrarily maintained for 3–6 months. The assumption here is that such patients have some anatomic or biochemical tendency toward thrombotic recurrence which may subside during long-term therapy. Since maintenance on heparin therapy is impractical, such individuals are switched to PTP drugs after the acute episode has subsided.

The comments above have outlined the standard therapeutic approaches. The fibrinolytic agents, however, may soon be regarded as desirable additions to the routine treatment of this disorder. Our studies thus far have indicated that a combined fibrinolytic-anticoagulant regimen is superior to anticoagulant therapy alone in several respects (55). The acute phlebitic signs and symptoms disappear more rapidly with corresponding reduction in duration of required bed rest, anticoagulant therapy and hospital stay. The incidence of pulmonary embolism and post-

thrombotic residuals appears to be reduced. Presently I recommend the use of a fibrinolysin-anticoagulant regimen in all cases of acute deep thrombophlebitis of less than 5 days' duration. In phlebitis of 5–10 days' duration, fibrinolysin seems less effective; and beyond 10 days, it seems of questionable additional benefit. I administer 100,000 units of the commercially available preparation intravenously over a 3- to 4- hour period as soon as the diagnosis is established. Heparin is then begun and maintained as described previously. If significant evidence of phlebitic activity persists after 24 hours, a second infusion of 50,000–100,000 units is given. The only patients in whom fibrinolytic therapy is contraindicated are those in whom anticoagulant drugs are also contraindicated or in whom a temperature elevation might be detrimental.

While our studies have led us to regard fibrinolysin as a valuable adjunct to standard therapy, there is need for further investigation before the value of this new therapeutic approach can be considered as established. Undoubtedly, more ideal agents and more efficacious dosage schedules will be devised in the future. The physician must make his own decision as to when the evidence warrants the use of fibrinolysin in his patients with deep thrombophlebitis. However, such decisions should be made promptly in each case, since, as I have indicated, fibrinolysin is most effective in dissolving fresh thrombi. The use of new drugs as a last resort after some days or weeks have passed will yield little benefit and will not provide a valid test of their effectiveness.

Acute Cerebrovascular Disorders

It seems advisable to divide the discussion of antithrombotic therapy in acute cerebral vascular disease into two sections: the first dealing with the so-called insufficiency syndromes and the second with the other types of vascular accidents. The present ideas regarding the therapy of these two forms of cerebral vascular disease differ considerably.

Insufficiency syndromes.—The features of the insufficiency syndromes have been described adequately elsewhere (56, 57). One's therapeutic attitudes toward these disorders are conditioned by one's views as to their etiology and prognosis as well as their

accessibility to surgical attack. The goal of all therapy is the same: to interrupt attacks and prevent permanent neurologic residual by ensuring vascular patency.

On the basis of available information it appears that basilar artery insufficiency (and other forms not susceptible to surgical correction) are best treated by anticoagulant therapy. In theory, if bouts of insufficiency are due to recurrent build-up and release of thrombi, such therapy should interrupt this sequence. In practice, anticoagulant drugs have proved beneficial, whether or not this hypothesis is correct. Furthermore, little risk accompanies anticoagulant therapy in this situation. Presumably, anticoagulant therapy should be a lifetime affair, once begun for an insufficiency syndrome, although long asymptomatic periods may be sufficient grounds for interrupting treatment. Again, heparin would appear to be the drug of choice for initial treatment, with subsequent transition to the PTP drugs for maintenance.

Internal carotid insufficiency can be corrected surgically when angiographic studies indicate the feasibility of such an approach and neurosurgical facilities are available. However, when surgical attack is not feasible for any reason, or will be delayed, anticoagulant therapy should be instituted promptly. Delay while awaiting surgery may be regretted. Since heparin effect can be interrupted rapidly, it constitutes no barrier to subsequent surgical procedures.

The use of the fibrinolytic agents in these disorders is still in the investigative stage. Experience thus far suggests that they will have a place in the immediate treatment of patients with insufficiency syndromes. I have observed coincident improvement in ophthalmodynametric readings and clinical status in several instances of internal carotid insufficiency following administration of Actase by the intravenous route. I have also observed improvement in the *pressure readings without* clinical improvement in patients seen shortly after onset of gross neurological abnormalities, suggesting that clot dissolution was achieved too late to permit functional return of damaged areas.

CEREBROVASCULAR ACCIDENTS.—The treatment of patients with cerebrovascular accidents leading to gross neurological deficit which do not fall into the insufficiency category is a difficult problem. Since surgical intervention is rarely feasible, the only recourse is to medical therapy. However, the routine use of anti-

thrombotic drugs has not been generally advocated, for at least three reasons: (1) cerebral hemorrhage cannot be readily differentiated from thrombotic or embolic disease even in the best hands; (2) even if angiograms demonstrate cerebral vascular occlusion, we cannot define whether the occlusion is due to clot, plaque rupture or subintimal hemorrhage; and (3) there is experimental evidence which questions the safety and value of antithrombotic drugs even in the presence of known cerebral thrombosis or embolism (58).

Despite such considerations, I believe that antithrombotic drugs deserve thorough evaluation in cerebrovascular disorders for the following reasons: (1) the morbidity and mortality which accompany supportive therapy alone justify exploration of all rational therapeutic maneuvers; (2) thrombosis accounts for a sizable proportion of cerebrovascular accidents, and the *early* use of antithrombotic drugs in such situations apparently is not associated with an increased risk of local hemorrhage. Therefore, during the last several years I have investigated the effects of heparin, PTP drugs and the fibrinolytic agents in a number of patients with sudden onset of extensive neurological deficit. In applying such therapy, I have attempted to exclude the patients with intracerebral hemorrhage by omitting those who demonstrated significant diastolic hypertension (above 110 mm. Hg), convulsions or severe headache, elevated cerebrospinal fluid pressure, hemorrhagic spinal fluid or rapid progression of neurological deficit. Angiographic study, when available, was used as supplemental evidence of pathogenesis.

The results obtained thus far have indicated that application of antithrombotic therapy in such patients is not a harmful procedure. In those who succumbed to their disease, I have rarely observed postmortem evidence suggesting that intracerebral bleeding was enhanced by such therapy. Meaningful data regarding improvement in morbidity or mortality rates cannot be supplied without a control group, but antithrombotic therapy has not provoked an evident increase in either. Therefore, I feel that such therapy can be applied with some assurance that it will rarely do harm. Proof that the fibrinolytic agents or anticoagulant drugs will help, however, obviously will require controlled studies. Thus the use of antithrombotic drugs in patients with acute cerebro-

vascular insults remains a matter for individual decision. The combination of prompt fibrinolytic therapy with the anticoagulant drugs offers a promising new therapeutic approach. Whether restoration of blood flow can be accomplished within the critical time limits imposed by the sensitivity of brain tissue to nutrient lack is open to question.

Peripheral Arterial Occlusion

There is currently little debate regarding the need for antithrombotic therapy in acute peripheral arterial occlusion. Heparin is again the drug of choice because of its rapid onset of action.

The feasibility of direct surgical attack should be promptly determined. While this possibility is explored, heparin should be administered by the intravenous or subcutaneous route. If surgery is elected, such therapy can be promptly interrupted.

In the acute situation, the fibrinolytic agents also may prove of value. "Medical" clot removal has advantages, since these patients often are poor surgical risks owing to the frequency of significant associated diseases. My experience to date with the available fibrinolysin-activator preparation has been most encouraging (43). Use of this fibrinolytic agent by intravenous or intra-arterial injection, followed by heparin therapy, has been associated with restoration of blood flow in a greater percentage of patients than might be expected to recover spontaneously (59). The fibrinolytic preparation has been administered in large initial doses (at least 150,000 fibrinolytic units of the commercially available agent). If improvement is not apparent in 3–6 hours, this dose is repeated. Subsequent administration is determined by the clinical response. Rarely have I had successful results in patients who failed to improve after three such doses at 6-hour intervals.

Since no fibrinolytic preparation has been released for the treatment of arterial diseases, the use of these preparations remains an academic consideration for most physicians. However, I can envision the ultimate regimen in acute arterial occlusion as evolving in the following manner: All patients will receive immediate combined therapy with a fibrinolytic agent and heparin. Where direct surgical attack is not feasible or is unavailable, this treatment will be continued. Where surgery can be applied, the effect

of antithrombotic treatment will be observed over a short (3–6 hour) period. If response in this interval is unsatisfactory, surgery will be carried out with the likelihood that the extent of thrombosis (or clotting subsequent to embolus lodgement) has been diminished.

It need hardly be stated that this "treatment protocol of the future" will not be applicable in all situations. Immediate surgical attack will remain the treatment of choice in certain instances. But if fibrinolytic agents fulfill their early promise in these disorders, our ability to deal with acute arterial occlusion will unquestionably be broadened and rendered more flexible.

SPECIAL CONSIDERATIONS

In this final section, a few comments will be made regarding certain questions which frequently arise when antithrombotic therapy is employed.

Contraindications

The only absolute contraindications to antithrombotic therapy are actual bleeding and the presence of significant hemorrhagic diatheses. All other contraindications (cachexia, hepatorenal disease, etc.) are relative and must be weighed against the possible benefits of anticoagulant therapy. For example, the patient with a known duodenal ulcer who develops venous thromboembolism usually merits anticoagulant treatment despite the risk involved. Heparin therapy, which can be rapidly interrupted, would be the best choice in such a situation. Obviously, close observation would also be mandatory. The use of either the fibrinolytic agents with their fibrin-dissolving capacity or the prothrombinopenic agents with their long duration of activity would appear less wise.

The pregnant woman requiring antithrombotic drugs also poses a problem, especially if she is near term. While decisions must be individualized, all of the antithrombotic agents have been used immediately before and after parturition without injury to mother or baby. Indeed, they often have been in effect during labor itself without complication. However, vitamin K_1 should be given

promptly to infants born while the mother is receiving PTP drugs and nursing is best omitted until therapy is interrupted.

The need for surgery during antithrombotic therapy often causes concern. It has been demonstrated that even major surgery can be safely carried out with these drugs in effect—indeed, such a course has been recommended by some to prevent postoperative thromboembolism. Presently, I prefer to interrupt such therapy during surgery itself, but this preference may prove unduly conservative. In vascular surgery—especially when porous grafts are used—antithrombotic drugs are likely best omitted for several hours to assure adequate fibrin deposition at suture lines.

All of these specific examples are variations on the same basic theme; viz., in the presence of any relative contraindication the risks must be weighed, and if they favor the use of antithrombotic drugs, therapy should be instituted with appropriate safeguards. The greatest safeguard is adequate knowledge of the agent being used.

Tapering of Therapy

The present consensus appears to support the idea that abrupt cessation of anticoagulant therapy should be avoided wherever possible. The fear of sudden cessation is that it may lead to some rebound phenomenon favoring thrombosis. While there are only a few data to support this fear, I have observed thrombotic recurrence after sudden cessation often enough to warrant the conservatism of a tapering procedure until the question can be settled.

Heparin and the Prothrombin Time

I should like to re-emphasize here that administration of heparin can prolong the one-stage prothrombin time. It is important to recall this fact when transition from heparin to a PTP drug is being made, since *heparin-induced prolongation of the prothrombin time may lead to cessation of heparin before the patient is actually "in range" with the PTP drug.* The patient is thus left relatively unprotected when heparin is discontinued. To avoid such errors, the blood for prothrombin tests should be drawn when heparin activity is at low ebb—e.g., shortly before the next sched-

uled dose when any usual intermittent schedule of heparin administration is being employed.

Antidotes

Three situations may call for partial or complete inhibition of anticoagulant or fibrinolytic effects: (1) overt bleeding during therapy; (2) more severe disturbance in coagulation than is considered safe; or (3) special problems, such as emergency surgery, trauma or parturition (see above). Each situation and each drug requires different action (60).

The actions of heparin can be promptly reversed by intravenous administration of protamine sulfate, which exerts a milligram-for-milligram inhibitory effect upon heparin. Since protamine actions persist for only 2–3 hours, repetition occasionally is required. Toluidine blue, which functions in a similar manner, exerts a less rapid but more prolonged inhibitory effect. These inhibitors are rarely necessary when the only abnormality is excessive prolongation of the clotting time. Unless large doses of heparin have been administered by the subcutaneous or intramuscular route, the clotting time shortly returns toward normal, so that simple omission or decrease in size of the next dose is all that is necessary. If prolongation of clotting time is extreme and yet continued anticoagulant effects are desired, small doses of protamine (5–30 mg.) are sufficient to reduce the excessive heparin activity. However, if active bleeding occurs, full inhibition should be carried out promptly.

Because the coagulation defects imposed by the PTP agents persist for many hours, they more frequently require specific inhibitory maneuvers. Two methods are available for this purpose: the administration of fresh whole blood and the administration of vitamin K_1 or menadione.

If active bleeding is present, whole-blood transfusions should be used to achieve rapid and complete restoration of the deficient coagulation factors. Vitamin K_1 (fat soluble) can be given simultaneously. If abnormal prolongation of prothrombin time exists without bleeding, the situation is different: blood or plasma is not indicated. Furthermore, administration of large doses of vitamin K_1 (50–150 mg.) not only will restore the prothrombin time

to normal but also will block the action of prothrombinopenic drugs for 4–6 days. Therefore, if one desires to continue therapy, small doses of vitamin K_1 (2.5–10) mg.) should be given intravenously or by mouth. Such doses will bring the patient back "in range" but will not interfere with continuation of treatment.

I have not yet found it necessary to inhibit the fibrinolytic agents in a clinical situation. However, the administration of fresh blood or plasma should satisfactorily remedy overdosage with these drugs. If massive doses have been given, fibrinogen administration might be required, and fibrinogen should be at hand if large doses are contemplated. Several specific inhibitors of fibrinolytic activity are also now available. The best studied of these is epsilon-aminocaproic acid (EACA). While the mechanism by which it acts is presently not fully elucidated, EACA appears to be a satisfactory antidote to excessive fibrinolysis when administered by the intravenous route.

"Which Is Best?"

I should like to end this monograph by attempting to answer a question which is often posed to me: viz., "Which type of agent most effectively blocks thrombus development—heparin or the prothrombinopenic drugs?" On the basis of my own experience and such experimental evidence as is available, I presently believe that heparin more adequately blocks the progress or development of thrombotic disease than do the PTP agents. The diffuse effects of heparin on various phases of coagulation also appear to confer some theoretical superiority on it. Therefore, I tend to rely on heparin for acute therapy in active thromboembolism and on the PTP drugs primarily for maintenance or prophylactic purposes.

As regards the fibrinolytic agents, their ultimate role remains to be defined. At the very least, however, the introduction of these agents has added new perspective to the study of thromboembolism and stimulated reappraisal of present therapeutic approaches.

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